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The impact of conisation on pregnancy outcome

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Summary

Aim: The objective of present study was to investigate whether conisation is associated with adverse pregnancy outcomes in Flanders, Belgium. Therefore a retrospective cohort study was conducted at the Antwerp University Hospital. *Materials and Methods:* The study was approved by the Ethical Committee and based on a questionnaire as well as on medical records. Confounders, like smoking, alcohol use, drug use, chronic illness, and gynaecological disorders during pregnancy were all taken into account. A multiple logistic regression was performed for an association between adverse pregnancy outcomes and confounders. *Results:* The study showed that there was association between conisation, low birth weight, and caesarean section. After conisation there was a significantly higher risk of 3.275 on a low birth weight. The risk of a caesarean section after conisation was tripled. A gynaecological disorder during the pregnancy had a significantly higher risk of delivering a child with a low birth weight and a higher risk of a caesarean section. Smoking and a chronic illness gave a significant higher risk of caesarean section. *Discussion:* Conisation is easy to perform and highly effective in the prevention of cervical cancer. Conisation has a high morbidity, as it is associated with severe adverse pregnancy outcome. A conisation should therefore only be performed on a true indication; otherwise it will be the victim of its own success.

Key words: HPV; Conisation; Preterm delivery; Adverse pregnancy outcomes; Vaccination; Cancer; CIN; HSIL; LSIL; Morbidity; Caesarean; Low-birth weight.

Introduction

The prevalence of human papillomavirus (HPV) in women with normal cervical cytology is worldwide estimated at 10.4%, with a 95 confidence interval of 10.2 % to 10.7 % [1]. The prevalence of HPV in cancer varies depending on geographic location and nature of the lesions [1-4] (Table 1). The five most common HPV types in cervical cancer are HPV16, HPV18, HPV45, HPV33, and HPV31 [2-6].

The cytological abnormalities have various categories. These include atypical squamous cells of undefined significance (ASC-US), atypical glandular cells (AGC), low grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), and atypical squamous cells with HSIL cannot be excluded (ASC-H) [2, 7] (Table 2).

The majority of the LSIL lesions (80%) will regress within in two years. About one quarter of the high-grade lesions slowly progress and may become invasive if left untreated [8-10]. Therefore HSIL lesions are generally treated by resection under local anaesthesia in women older than 25 years. When CIN1 is detected, follow-up is advised, since these lesions will disappear in 90% of cases without any treatment within two years [11]. The remaining 10% may be persistent LSIL or progress to HSIL over time [8-14]. Considering the majority of lesions (80%) regress spontaneously, it is advised to postpone screening women under 25 years to prevent over-treatment and avoid anxiety [7].

In Flanders a vaccination program for HPV was started in September 2011, namely with Gardasil which is highly effective against HPV types 6, 11, 16, 18, and 31. In Wallonia, vaccination started in September 2012 with Cervarix, which has a significant protection against HPV types 16, 18, 31, 33, 45, 51, and 56 [15]. In women naive of all HPV types, Cervarix has a moderate efficacy against a six-month persistent infection with HPV 6, 53, or 74 [15].

The abnormal tissue can be removed by a conisation. A conisation can be performed by cold knife, laser or with very thin loop called LLETZ of LEEP (which means respectively a large loop excision of the transformation zone or a large endocervical excision procedure [16-21]. The last 20 years LLETZ/LEEP is primarily used. This procedure has several advantages compared to other techniques: it is an inexpensive technique and is relatively easy to learn and it can be done under local anaesthesia in an outpatient setting. The U-or V-shaped loop used in the procedure consists of stainless steel or titanium. Different loop sizes are available, which allows size adjustment. During the procedure an electrical power will be sent through the loop, which will allow excising the affected tissue. The main advantage is that the removed tissue can be examined histologically. The precise diagnosis, the completeness of the excision, and the margin can therefore be determined [22].

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Table 1. — *Prevalence HPV.*

HPV type	Normal cytological tissue (World)	High-grade lesions (Europe)	Invasive cervical carcinoma (World)	Invasive cervical carcinoma (Europe)	Invasive cervical carcinoma (Belgium)
HPV 16	2.5%	57.4%	61%	62.6%	68.7%
HPV 18	0.9%	5.5%	10%	14.6%	12.3%
HPV 31	0.7%	12.4%	4%	4.3%	6.2%
HPV 58	0.6%				
HPV 52	0.6%	7.4%		2.5%	
HPV 45		3.4%	6%	6.3%	1.8%
HPV 33		12%	3%	5.2%	5.3%

Table 2. — *Prevalence of HPV in various categories.*

Cytological abnormalities	Prevalence of HPV (%)
ASC-US	77
AGC	32
LSIL	85
HSIL	93
ASC-H	93

Aim of this study

The cytological changes occur mainly in women in their reproductive age. Therefore, treatment is nowadays often needed before pregnancy desire is fulfilled. Studies showed that LLETZ/LOOP gives an increased risk on preterm delivery (gestational age < 37 weeks) and premature rupture of membranes. It is also associated with a slightly increased risk on a short delivery (< two hours) and no increased risk on caesarean section. There is also a higher risk on both low birth weight (< 2,500 grams) and perinatal mortality [23]. The objective of this study was to determine whether this association is also present in Flanders.

In present study as in previous studies, efforts were made to take other factors into consideration that may have adverse effects on the pregnancy including smoking, alcohol use, cardiovascular disease, chronic diseases, infections, multiple pregnancies, and (pre) eclampsia [24, 25]. In reality, it is however almost impossible to take all these variables into account. Nevertheless efforts were made to measure them.

Materials and Methods

In this study, data from women who have recently given birth are analysed. The study population includes women with an age between 16 and 50 years. Other inclusion criteria were a gestational age from 24 weeks until 42 weeks and a conisation according to LLETZ/LEEP. Exclusion criteria included multiple pregnancies and the absence of the required data. The required information, such as gestational age, birth weight, delivery method, and duration of labour, came from the Standardized Obstetric and Perinatal Record of the digital medical file and a questionnaire. The questionnaire obtained additional information about the lifestyle of the woman and whether a conisation had occurred in the past. The ethical committee of the Antwerp University Hospital approved the study protocol on December 5, 2011, with reference number 11/25/192. JMA and FA conducted the questionnaire in a standardized way. Before the interview took place, the aim of the study was described in simple terms. After the informed consent was obtained and signed, the interview took place. An information brochure, that contained contact details of the researchers, was given to each participating woman. In case there were uncertainties, questions or requests to terminate participation in the study, there was always the possibility to contact one of the researchers. The data from the Standardized Obstetric and Perinatal Record and the questionnaire were combined in an Excel document.

The women were divided into two groups, namely a cohort of women who had undergone conisation and a cohort of women who had not undergone a conisation. The data from the Excel document was statistically analysed using SPSS 22, to determine whether there was a difference in the incidence of adverse pregnancy outcomes between the two cohorts. As required the data were encrypted, in order to prevent connecting the date directly or indirectly to a person. A multiple logistic regression was conducted to investigate the role of the different variables especially smoking, alcohol consumption, drug use, chronic disease, gynaecological disorders during pregnancy, and conisation on pregnancy outcomes.

The pregnancy outcomes include premature birth, low birth weight, perinatal mortality, premature rupture of the membranes (PROM), caesarean section, and short delivery.

Results

Weekly interviews were conducted at the maternity ward of the Antwerp University Hospital. These interviews were conducted over a two-year period, between March 2012 and March 2014. During that period an attempt was made to interview 370 women. Seventeen women did not participate in the study because of refusing to be involved or due to a language barrier; 353 women agreed to participate and the questionnaire was conducted. All the additional needed information from these women was extracted from the Standardized Obstetric and Perinatal Record. Ten of the participating women had to be excluded from the study due to inability to find sufficient information in the Standardized Obstetric and Perinatal Record. The data of the 343 included women was statistically analysed. None of the woman answered affirmatively when questioned about drug use, that is why the confounder drug use was not included in the statistical analysis (Figure 1).

Association between conisation and adverse pregnancy outcomes

The women were divided into a cohort of women who have undergone a conisation and into a cohort of women who have not undergone a conisation. The cohort who included women who had a conisation in the past contained 18 women. The cohort of women who have not undergone a conisation included 325 women. In the study population, preterm delivery occurred 70 times, a low birth weight 13 times, a caesarean section 118 times, and perinatal mortality and short delivery both twice.

Table 3. — *Prevalence of adverse pregnancy outcomes.*

	Preterm delivery		Low birth weight		Caesarean section		PROM		Perinatal mortality		Short delivery	
Conisation	0	1	0	1	0	1	0	1	0	1	0	1
0	80.3%	19.7%	80.9%	19.1%	66.8%	33.2%	96%	4%	99.4%	0.6%	99.4%	0.6%
1	66.7%	33.3%	61.1%	38.9%	44.4%	55.6%	100%	0%	100%	0%	100%	0%

0 = present; 1= absent.

Table 4. — *Multiple logistic regression.*

	Preterm delivery				Low birth weight				Caesarean section			
	Sig	Exp(B)	95% CI for Exp(B)		Sig	Exp(B)	95% CI for Exp(B)		Sig	Exp(B)	95% CI for Exp(B)	
			Upper	Lower			Upper	Lower			Upper	Lower
Smoking	0.745	1.194	0.410	3.483	0.735	1.205	0.409	3.545	0.041	**0.266**	0.075	0.948
Alcohol	0.647	0.862	0.456	1.630	0.284	0.695	0.358	1.351	0.422	0.800	0.464	1.380
Chronic disorder	0.198	1.963	0.703	5.481	0.192	1.986	0.708	5.569	0.041	**2.645**	1.039	6.737
Gynaecological	0.001	**2.954**	1.590	5.489	0.001	**2.840**	1.515	5.323	0.044	**1.810**	1.016	3.224
Conisation	0.115	2.345	0.812	6.771	0.024	**3.275**	1.171	9.158	0.027	**3.090**	1.140	8.370

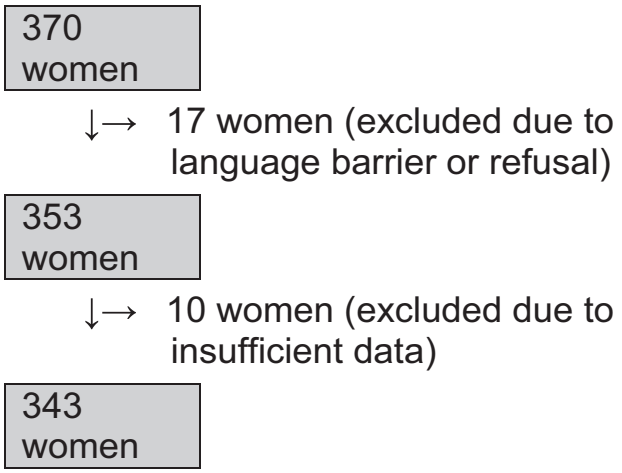

Figure 1. — Study cohort and exclusion criteria.

Table 5. — *Backwards stepwise (conditional): low birth weight.*

		Sig.	Exp(B)	95% C.I.for EXP(B)	
				Lower	Upper
Step 1	Smoking	0.735	1.205	0.409	3.545
	Alcohol	0.284	0.695	0.358	1.351
	Chronic disorder	0.192	1.986	0.708	5.569
	Gynaecological disorder	0.001	2.840	1.515	5.323
	Conisation	0.024	3.275	1.171	9.158
Step 2	Alcohol	0.287	0.697	0.359	1.355
	Chronic disorder	0.194	1.981	0.706	5.556
	Gynaecological disorder	0.001	2.832	1.512	5.305
	Conisation	0.022	3.307	1.187	9.217
Step 3	Chronic disorder	0.186	2.007	0.714	5.638
	Gynaecological disorder	0.001	2.758	1.476	5.153
	Conisation	0.031	3.053	1.105	8.435
Step 4	Gynaecological disorder	0.002	2.677	1.441	4.972
	Conisation	0.031	3.010	1.103	8.217

Preterm delivery

Six out of 18 women who had undergone conisation delivered prematurely. The proportion of preterm delivery in women who had not undergone conisation was 19.7% (Table 3). The Chi-Square value was 1.954 and was expected to be higher than 3,67 and therefore a significant difference between both cohorts cannot be demonstrated. A multiple logistic regression was conducted to investigate the impact of lifestyle on the gestational age. Gynaecological disorders during pregnancy gave a significant higher risk on preterm delivery, with an increase in risk of 2.94. Smoking, use of alcohol, chronic disorders, and conisation did not give a higher risk on preterm delivery (Table 4).

Low birth weight

In the cohort of woman who had undergone a conisation, seven out of 18 children (38.9%) had a low birth weight. The proportion of a low birth weight in the cohort of woman who have not undergone a conisation was six out of 325 (19.1%) (Table 3). The difference between the cohorts is significant, because the Chi-Square value is 4.166 and supposed to be higher than 3.62. The multiple logistic regression showed a significant higher risk of 3.275 on low birth weight after conisation. Gynaecological disorders during pregnancy gave a significant higher risk of 2.84 on low birth weight. Smoking, use of alcohol, and chronic disorders did not give a higher risk on low birth weight (Table 4). A backwards-stepwise analyses was conducted, which confirmed these results (Table 5).

Caesarean section

Ten out of 18 women (55,6%) who had undergone a conisation underwent a caesarean section. In the cohort of women who did not undergo a conisation, 108 out of 325

Table 6. — *Backwards stepwise (conditional): caesarean section.*

		Sig.	Exp(B)	95% C.I.for EXP(B)	
				Lower	Upper
Step 1	Smoking	0.041	0.266	0.075	0.948
	Alcohol	0.422	0.800	0.464	1.380
	Chronic disorder	0.041	2.645	1.039	6.737
	Gynaecological disorder	0.044	1.810	1.016	3.224
	Conisation	0.027	3.090	1.140	8.370
Step 2	Smoking	0.040	0.264	.074	0.938
	Chronic disorder	0.039	2.671	1.049	6.805
	Gynaecological disorder	0.049	1.783	1.003	3.169
	Conisation	0.032	2.948	1.096	7.928

women (33.2%) had to give birth by caesarean section (Table 3). This difference is not significant. The Chi-Square value was 3.767 and the minimal value had to be 6.19. The multiple logistic regression showed a significant higher risk of 0.2 on caesarean section after smoking. There was also a significant higher risk of 2.645 in the presence of a chronic disease. The regression also showed a significant higher risk on caesarean section in a gynaecological disorder and following a conisation, 1.81 and 3.09 respectively (Table 4). A backwards-stepwise analyses was conducted and confirmed these findings (Table 6).

PROM, perinatal mortality and short delivery

In the cohort consisting of women who underwent conisation: PROM, perinatal mortality, and short delivery did not occur. In the cohort with women who did not undergo a conisation, PROM occurred in 13 out of 325 women. Perinatal mortality and short delivery occurred twice (Table 3).

Discussion

Cervical cancer screening is recommended for women between the ages of 25 and 65 [7]. Nevertheless 10% of the screened women are younger than 25 years of age and 7% are older than 65 [7]. In Belgium screening outside the recommended age group of women costs the medical insurance 12 million Euro per year [7]. Most precancerous lesions (80%), LSIL as HSIL in women younger then 25 years disappear spontaneously within two years. Detection of these precancerous lesions in this age group leads to unnecessary anxiety and also to over-treatment. Regardless of age, LSIL lesions will regress in 90 % of the cases [11]. Conisation is an easy to learn and often used technique in women who still have a child wish. Therefore a conisation should from a clinical point of view only be used for HSIL or AGC lesions.

In this study a significantly higher risk on adverse pregnancy outcomes was found after conisation, especially for low birth weight and caesarean section. A gynaecological disorder and a conisation gave a significantly higher risk on a low birth weight. Present study showed that the risk on a caesarean section after conisation was tripled. Other studies however did not find this significant high risk [26-28]. The correlation between conisation and the risk on low birth weight was also present in three other studies. In those studies, the risk on low birth weight after conisation was doubled and nearly tripled [26-28]. In present study the risk on low birth weight after conisation was more than tripled. Smoking, a chronic disorder and a gynaecological disorder during pregnancy caused a significant higher risk on a caesarean section.

Present study, as also in the study by Werner *et al.* did not show significant correlation between conisation and preterm delivery [29]. This was rather surprisingly and there are three other studies however that found a double and even triple association between conisation and preterm delivery [26, 27, 30].

The explanation why in the present study there was no association between conisation and preterm delivery is the small proportion of women who underwent a conisation. The population was simply too small to create significant result. The opinion exists that had the cohort of women with a conisation been larger, there would have been a significant higher risk on preterm delivery. An interim analysis was conducted. In comparing the interim analyses with the end results, it is very clear that the results become more statistically relevant. A further drawback of this study is that the Chi-Square test is not reliable because of the small cohorts. More value can be attached to the outcomes of the multiple logistic regression. Some reservations can be made when looking into the design of the study. For practical reasons the interviews at the maternity ward of the Antwerp University Hospital were conducted once a week. That made it impossible to interview all women who gave birth. Certain situations like perinatal mortality or serious health conditions of the mother or the neonate made conducting the interview not possible out of human consideration. A large proportion of the needed information came directly out of the questionnaire.

The veracity of the filled out questionnaire can be questioned. It is most certainly possible that women, who smoke, use alcohol or drugs during pregnancy are not honest about this. It is possible that those aspects of lifestyle will not be correctly filled out in the questionnaire, because most women are aware of the adverse impact on pregnancy outcomes. It is also highly unlikely that none of the 343 included women had used drugs during their pregnancy.

It was difficult for the women who had undergone a procedure to recall what kind of procedure was executed. Most of the women who had undergone a conisation were not aware which technique was used to remove the affected cervical tissue. The information about the used conisation technique was not present in the medical record, given that

the conisation took mostly place in a different hospital. Thereby it was also impossible to determine which cone size or volume was removed. The cone size/volume has an effect on the extent of the risk on adverse pregnancy outcomes, especially on preterm delivery and PROM [26, 27, 30, 31].

Smoking, use of alcohol, cardiovascular disease, chronic disorders, infections, multiple pregnancy, and pre-eclampsia have adverse effects on the pregnancy [24, 25]. Other studies were not able to take these confounders sufficiently into account [31]. This study endeavoured to take these confounders into account. The conviction exists that had the study population been larger, more clinically significant results would have emerged. Ideally conisation, pregnancy follow-up, and delivery should have been in the same hospital. A request had been made to the Flanders's Study Centrum for Perinatal Epidemiology [Vlaams Studiecentrum voor Perinatale Epidemiologie (SPE)] for the registration of conisation and their method. Rather surprisingly the SPE was not interested in adding these questions to their standard digital registration form.

The future for conisation-related morbidity looks fortunately more broad due the high vaccination coverage in Flanders. In Flanders more than 80% of the 12- and 13-year-old girls are vaccinated against HPV. This makes Flanders one of the best-vaccinated regions of the world. In 15 to 30 years the high number of vaccinated girls will most likely result in a noticeable reduction of precancerous (> 50%) and cancerous (>80%) lesions. A monovalent vaccine which is effective against HPV types 16, 18, 31, 33, 45, 52, 58, 6, and 11, is approved by the FDA and waiting for commercialisation [7]. The safety profile of the monovalent vaccine is similar in comparison to Cervarix. The monovalent vaccine is also very effective in preventing development of precancerous lesions. Approximately 94% of all cervical carcinoma's can possibly be prevented if the monovalent vaccine is used optimally [7]. The assumption can be made that there will be a reduction of conisations by more than 50%; this will result in a lesser amount of adverse pregnancy outcomes. Another important step will be the standardisation of HPV testing with attention for E6 and E7 [32, 33]. Knowledge is power. There can only be an improvement in attending screening and vaccination if every man, woman, and adolescent is informed on its own level [34] Further investigation of the effect of vaccination on preterm delivery and other adverse pregnancy by a National Registration could be useful. However there has to be the political and medical willingness and the money to organise this.

In conclusion, conisation is associated with serious adverse pregnancy outcomes. Screening for HPV in women between 25 and 65 years of age is recommended as well as universal HPV vaccination at adolescent age. HPV vaccination is not cost effective for a government at older age, however it can be considered as a private investment in one's own health. One should see it as a anti-virus program on one's own personal computer. The latter is also not reimbursed, but highly effective in daily life. In the near future the frequency of conisations and adverse pregnancy outcomes will diminish because of the effectiveness of the HPV vaccination programs.

A conisation is easy to perform and highly effective in the prevention of cervical cancer. However is has a high morbidity in terms of severe adverse pregnancy outcomes. A conisation should therefore only be performed only on true indications; otherwise it will be a victim of its own success.

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