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Natural History of Squamous Intraepithelial Lesions in Pregnancy and Mode of Delivery

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Abstract. *Background: Numerous studies have addressed the impact of mode of delivery on the natural history of squamous intraepithelial lesions (SIL) in pregnant women. However, the literature is still contradictory. Patients and Methods: In the course of a retrospective analysis, data of 63 pregnant women with abnormal cervical smears who were referred to our Outpatient Department for pre-invasive lesions of the cervix were analyzed. The study was conducted at the General Hospital in Vienna, Austria, between 2010 and 2015. Data collection included demographics, delivery route and diagnostic results of cervical lesions by cytology, colposcopy, human papilloma virus (HPV) testing, histological report of punch biopsy and, if applicable, cone biopsy. Results: Among 63 women who met the inclusion criteria, 40 (63%) delivered vaginally and 23 (37%) underwent caesarean section. Postpartum regression of cervical dysplasia was documented in 15 women delivering vaginally and in 10 who had a caesarean section (p=0.641). Among those women who delivered vaginally, three had progression and in 22 women the lesions persisted postpartum. In the group of women with caesarean section, one had progression and the lesions of 12 women persisted after delivery. No woman had progression to invasive disease. Conclusion: The mode of delivery does not significantly influence the natural history of cervical dysplastic lesions in pregnant women. The numbers of spontaneous regressions to normal cervical cytology during pregnancy were similar in both groups.*

Human papilloma virus infections are especially common among young women, occurring in about 25% of the 20- to 30-year age group. Moreover, these infections are an important factor contributing to the development of cervical cancer (1). The incidence of abnormal cervical smears and HPV infections has been reported to be 5-8% in pregnant as well as non-pregnant women (2-8).

About 30% of women diagnosed with cervical cancer are in their reproductive years (2). The majority of pregnancies occur between the ages of 18 and 35 years, corresponding to the age range associated with the greatest incidence of HPV infection and following cervical intraepithelial neoplasia (4, 9). This increasing trend may also be attributed to cervical cancer screening being an essential part of prenatal care (10).

Cervical cancer in pregnancy is estimated to have an incidence of 1-10/10,000 pregnancies, depending on the inclusion of carcinoma *in situ* and postpartum patients (2, 3). Approximately 3% of cervical cancer cases are diagnosed during pregnancy (2). Although cervical cancer in pregnant women is very rare, cervical precancerous lesions have been reported in 5% of all pregnancies (5, 8, 11).

Numerous studies showed that 10-70% of cervical squamous intraepithelial lesion cases in pregnant women regress and sometimes even disappear postpartum (3, 7, 8, 12-15), whereas persistence of CIN is reported in 25-47% of cases (3, 7, 13) and progression in 3-30% of cases (3, 12-14).

However, the impact of mode of delivery on the natural history of CIN lesions remains unclear.

Patients and Methods

Between 2010 and 2015, 63 pregnant women with abnormal PAP smear results who were referred to the Outpatient Department for pre-invasive lesions of the cervix at the General Hospital in Vienna, Austria, were identified through the medical records data repository. Even though there were more pregnant patients with atypical PAP smear results within this period, only 63 had a full data record and were therefore included in this study. One woman presented with invasive cervical cancer during pregnancy at the first visit and was therefore excluded from the study.

The patients had at least one examination, including amongst others cervical cytology, colposcopy, HPV testing and eventually biopsy, prior to delivery and a second examination 6 to 8 weeks postpartum.

The retrospective data review of the patients' medical records revealed age and gestational week at first examination, parity, smoking history during pregnancy, HPV vaccination status, HIV and hepatitis C status, mode of delivery, antepartum and postpartum

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diagnosis of cervical lesions by cervical cytology, cervical HPV testing and biopsy. Patients characteristics are displayed in Table I.

To determine the impact of the delivery route on the natural development of cervical dysplasia, the patients were analyzed in two groups: (i) vaginally delivering women and (ii) patients with caesarean section as mode of delivery.

The postpartum results were specified into progression, persistence and regression as determined by comparing the antepartum and postpartum cervical smear, categorized as negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesion (HSIL), and biopsy results, categorized as negative results, CIN1, 2 or 3, of the lesions (according to the terminology utilized at the study period for SIL at our Institution). The regression rates of cervical cytological and histological findings of the two groups were compared using the statistical analysis with IBM SPSS Statistics 24 (IBM Corp., Armonk, NY, USA). Pearson's chi-squared test, unless stated otherwise (level of significance: α=0.05).

Sociodemographic data were statistically analyzed by Pearson's chi-squared test or by the *t*-test for two independent samples in order to compare the two patient groups. *p*-Values of less than 0.05 were considered statistically significant.

Results

There were no statistically significant differences between the groups regarding age (p=0.95), gravidity (p=0.73), parity (p=0.46), smoking during pregnancy (p=0.417) and HPV infection status (p=0.161). Two (9%) females of the caesarean section cohort were HIV-positive. Three (13%) women who had a caesarean section and one (3%) who delivered vaginally tested positively for hepatitis C. A significantly higher number of HIV (p=0) and hepatitis C (p=0.001) cases in the caesarean section group was found (Table I). Only two (3%) patients were HPV-negative and only one (2%) has been vaccinated against HPV (Table I). Regardless of whether the women underwent cone biopsy or were treated conservatively, no statistically significant difference comparing the cohorts was found (p=0.554) (Table I). The cytological and histological results of both groups are demonstrated in Table II.

For comparing these rates between the cohorts, those with persistently negative biopsy and not assessable results were excluded, leading to a lower patient number of 25 (58.1%) women who delivered vaginally and 18 (41.9%) who underwent caesarean section.

Women with LSIL had the highest regression rate (44.4%) to NILM compared with ASC-US and HSIL antepartum results (Table III). Patients with CIN1 presented the highest regression rate (40%) to negative results compared to CIN2 and 3 antepartum results (ASCU-US: Atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL high-grade squamous intraepithelial lesion; AGC: atypical glandular cells; NILM: negative for intraepithelial lesion or malignancy (Table III).

Table I. *Patient characteristics*.

Characteristic	Mode of delivery	
	Vaginal delivery (n=40)	Caesarean section (n=23)
Age (years)		
Mean (SD)	29 (±5)	30 (±4)
Week of gestation at first examination during pregnancy		
Mean (SD)	16 (±7)	17 (±9)
Gravidity		
Mean (SD)	2 (±1)	2 (±1)
Parity		
Mean (SD)	2 (±1)	2 (±1)
Nicotine abuse, n (%)		
No	10 (25%)	3 (13%)
Yes	12 (30%)	6 (26%)
Not documented	18 (45%)	14 (61%)
Hepatitis C status, n (%)		
Negative	39 (97.5%)	20 (87%)
Positive	1 (2.5%)	3 (13%)
HIV status, n (%)		
Negative	40 (100%)	21 (91%)
Positive	0 (0%)	2 (9%)
HPV vaccination status, n (%)		
Not vaccinated	22 (55%)	15 (65%)
Vaccinated	1 (2.5%)	0 (0%)
Not documented	17 (42.5%)	8 (35%)
Result of HPV testing at first examination during pregnancy, n (%)		
Negative	1 (2.5%)	1 (4%)
High-risk positive	37 (92.5%)	21 (91%)
Not carried out	2 (5%)	1 (4%)
Subsequent procedure, n (%)		
Not documented	1 (2.5%)	0 (0%)
Cone biopsy	14 (35%)	10 (43%)
Conservative management	25 (62.5%)	13 (57%)

There was no statistically significant difference of regression to lower-grade smear results/negativity (p=0.641), nor in persistence (p=0.828) and progression (Fisher's exact test: p=0.535) rates of PAP smear results comparing the two groups (Table I).

No statistically significant difference in regression (p=0.553), persistence (p=0.405) and progression (Fisher's exact test: p=0.553) rates of biopsy results comparing the two study groups was found (Table IV). No woman had progression to invasive disease.

Discussion

Reports addressing the effects of the mode of delivery on the clinical course of cervical lesions during pregnancy and postpartum period are limited and contradictory.

Table II. *Distribution and natural history of PAP smear results and histological samples comparing the cohorts.*

Comparison of cohorts	Mode of delivery, n (%)	
	Vaginal delivery (n=40)	Caesarean section (n=23)
Cervical smear results		
Antepartum		
ASC-US	3 (7.5%)	3 (13%)
LSIL	26 (65%)	10 (43%)
HSIL	11 (27.5%)	10 (43%)
Postpartum		
NILM	14 (35%)	8 (35%)
ASC-US	3 (7.5%)	1 (4%)
LSIL	11 (27.5%)	7 (30%)
AGC	0 (0%)	1 (4%)
HSIL	12 (30%)	6 (26%)
Natural history		
Regression	15 (37.5%)	10 (43%)
Persistence	22 (55%)	12 (52%)
Progression	3 (7.5%)	1 (4%)
Histological samples		
Antepartum		
Negative	9 (22.5%)	2 (9%)
CIN1	5 (12.5%)	5 (22%)
CIN2	7 (17.5%)	6 (26%)
CIN3	13 (32.5%)	9 (39%)
No biopsy carried out	6 (15%)	1 (4%)
Postpartum		
Negative	19 (47.5%)	6 (26%)
CIN1	5 (12.5%)	3 (13%)
CIN2	4 (10%)	7 (30%)
CIN3	7 (17.5%)	3 (13%)
No biopsy carried out	5 (12.5%)	2 (9%)
Not assessable	0 (0%)	2 (9%)
Natural history		
Regression	12 (30%)	7 (30%)
Persistence	13 (32.5%)	9 (39%)
Including persistence of negative result	5 (12.5%)	1 (4%)
Progression	5 (12.5%)	3 (13%)
Not assessable	10 (25%)	4 (17%)

ASCU-US: Atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; AGC: atypical glandular cells; NILM: negative for intraepithelial lesion or malignancy; CIN1/2/3: cervical intraepithelial neoplasia grade 1/2/3.

Table III. *Natural history of cervical smear results of all study participants.*

Cervical smear results, n	Postpartum				
	NILM	ASC-US	LSIL	AGC	HSIL
Antepartum					
ASC-US (n=6)	2	0	3	0	1
LSIL (n=36)	16	2	14	1	3
HSIL (n=21)	4	2	1	0	14

ASCU-US: Atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; AGC: atypical glandular cells; NILM: negative for intraepithelial lesion or malignancy.

Table IV. *Natural history of histological samples of all study participants.*

Histological samples, n	Postpartum					
	Negative	CIN1	CIN2	CIN3	Not carried out	Not assessable
Antepartum						
Negative (n=11)	5	3	0	0	3	0
CIN1 (n=10)	4	3	2	0	0	1
CIN2 (n=13)	3	2	5	2	1	0
CIN3 (n=22)	8	0	3	8	2	1
Not carried out (n=7)	5	0	1	0	1	0

CIN1/2/3: Cervical intraepithelial neoplasia grade 1/2/3.

According to our study, the mode of delivery did not significantly influence the natural history of cervical precancerous lesions in the study population. This result correlates with findings of other previously conducted studies (11, 16-19). However, this is in contrast with the results of five other studies (10, 13, 20-22) which showed higher regression rates in women who delivered vaginally.

The examination procedure of our study included colposcopy and biopsy for almost all patients, however, Ahdoot *et al*. merely analyzed cytological data only (21). Furthermore, their degree of cervical dysplasia was unevenly distributed with 45% patients with HSIL, making the study population less representative for the general population than the findings of our study (33% with antepartum HSIL).

In our study population, the rate of HIV-infected females in the caesarean section group was significantly higher. HIV-positive women undergo caesarean section to protect the newborns from vertical transmission. As these women are more likely to have persistent cervical lesions, this could have served as a confounding factor.

The overall regression rates (cytological regression: 40%, histological regression: 30%) in our study population are similar to those reported in previous studies (3, 15, 23, 24). Chung *et al*. reported a total regression rate of 92.9% which is much higher than the one found in our study (10). The small population of both studies is taken into account for such different findings. Additionally, sampling errors of

biopsy and subsequent failed identification of more severe lesions are possible.

The retrospective aspect of the study also probably limits the general applicability of the results. However, it is difficult to conduct a prospective randomized trial as the obstetrical history has to be taken into consideration.

Nonetheless, our study results are hypothesis-generating and compelling. They support the need for a prospective study with a larger population to affirm these significant clinical implications so that pregnant women suffering from CIN can be counselled and treated properly. The diagnosis of CIN during pregnancy can cause anxiety and concern in the expectant mother. Thus, explaining the pathogenesis and treatment options of cervical lesions and the possibility of both delivery modes, vaginally and by caesarean section, is an important tool for patient's compliance.

In conclusion, our retrospective results suggest that the mode of delivery does not significantly influence the natural history of cervical dysplasia in pregnant women. The objective of patient care is to continue the pregnancy and exclude invasive disease.

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