

Progression Risk of Epithelial Lesions of Cervix in Pregnant Women, Youth Island, 2014–2017

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ABSTRACT

Due to the general tendency of postponing the reproductive stage to superior ages and the effect of the techniques of attended reproduction, the coincidence of cancer and pregnancy is supposing an increment, as well as of its lesions precursors. This prospective descriptive study was conducted to determine the statistical relationship between the progression of epithelial cervical lesions and clinicoepidemiological factors of interest in 131 pregnant women assisted in the General Educational Hospital “Baire Heroes” during the period 2014-2017. Nearly 61% of the patients were in the age group of 20-29 years, 42% of antecedents referred 1-2 previous pregnancies, 74% used intrauterine devices, 37% had precocious menarquia before 13 years of age, 32% began sexual relationships before 15 years of age, and negative cytology or with lesions of low degree was present in 71% of the studied sample. The histology of CIN2+, lesion in cervical channel, +2 sexual couples in last 5 years, lesion >149mm², persistent infection by human papilloma virus (IHPV), age younger than 20 years, lesion in anterior lip or both lips and corners, cytology with high-grade squamous intraepithelial lesion/cancer, parity >1, abortions >2 and the first sexual relationship before 15 years of age showed significant statistical difference among the cases in that progression of the lesions epithelial was identified. The presence of CIN2+, lesion in cervical channel, lesion >149mm², persistent IHPV and age smaller than 20 years meant a probability of progression of 93%.

Key words: cancer, pregnant, progression

INTRODUCTION

Cancer is a strange condition during pregnancy. This coincidence is estimated in one of each 1000 gestaciones.^[1] Every year, between 3500 and 6000 new cases of wicked illnesses are diagnosed in the United States, representing the third part of the maternal deaths.^[2]

Due to the general tendency of postponing the reproductive stage to superior ages and the effect of the techniques of attended reproduction, the cancer coincidence and pregnancy is supposing an increment, as well as of its precursors lesions. According to Yamasaki^[3] in a revision article, Jolles mentions that the severe dysplasia of the cervix can reach frequencies of 26 cases for a thousand births, as well as five cases of carcinoma *in situ* for a thousand pregnant cases.

Although recent studies have refuted the idea that cancer has worse answer and presage during the gestation when compared with non-pregnant women, it continues being a challenge for oncologists and obstetricians to provide the best treatment to this singular patient, that doesn't affect to the fetus.^[4]

Existent studies of the natural history of cervical intraepithelial neoplasia (CIN) are limited by several factors: (1) The confirmation of diagnosis and definitive classification of the CIN requires biopsy, but this can alter its natural history, perhaps for induction of a local inflammatory reaction. Some studies, to avoid this possibility, carry out the diagnosis by examination of the cells; but even in combination with the colposcopy, this focus can cause false-positive and false-negative reinforcements, with the subsequent overestimation or underestimation of the progression potential; (2) The duration

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of the pursuit because the progression toward the invasive cancer requires years, especially in the early lesions, and because numerous patients with irregular pursuit return to this uncertain factor; (3) A factor that can confuse the interpretation of the natural history is the heterogeneity of some CIN; the colposcopy with direct biopsy cannot cover significant lesions and errors of sampling may take place classifying some patients erroneously, with a substantial impact for the progression or regression of the illness; (4) Another factor of confusion is the different interpretation of the lesions on the part of the pathologist; (5) The age can modify the progression risk inside CIN degree. The immunity variability for local or individual factors, such as infection for the human immunodeficiency virus (HIV) or renal implants, can increase the progression.

In the Youth's Island, with a global tendency to the increment in the last 15 years, were diagnosed nearly 40% of all cases of the period 2003–2016 during the triennium 2014–2016, nearly 57% of them have been diagnosed in patients younger than 30 years (data of the author),^[5-7] So, this phenomenon shows medical situations as the attention to pregnant and patient without satisfied parity.

The contribution of this investigation can constitute a vital tool to take decisions before one of the common dilemmas to the topic: what to make with a pregnant with lesion cervical epithelial that doesn't owe conizate but to guarantee a sure pursuit. On the other hand, the study of these variables allows to deepen the knowledge that every day arises in this respect, since there were no enough studies in the country that deepen specifically on this topic, which will not only offer a therapeutic contribution, but also diagnose this pathology. From the methodological point of view, the present investigation will be a good starting point to other investigators to elaborate future studies related to this topic, and it would also allow to this institution to offer them more and better treatment alternatives to the patients that consult for this pathology, diminishing the unnecessary interruption of gestations and to improve the quality of the population's life.

GENERAL OBJECTIVE

The objective of this study was to identify the relationship between the progression of epithelial lesions of the cervix and clinicoepidemiological factors of interest in pregnant women assisted in the Hospital General Educational "Baire Heroes" during 2014–2017.

GOALS AND OBJECTIVES

1. To describe the distribution of variables such as age groups, previous gestations, factors related with the sexual life, and cytological diagnosis.

2. To identify the presence of progression of predictive factors in the study sample.
3. To design a prediction model starting from the identified factors.

DESIGN METHODOLOGICAL

This prospective descriptive study was carried out to determine the statistical relationship between the progression of cervical epithelial lesions and clinicoepidemiological factors of interest among 131 pregnant women assisted in the General Educational Hospital "Baire Heroes" during 2014–2017 that satisfied the inclusion criteria:

- Pregnant women assisted in this institution.
- Pregnant women with cytological diagnosis of low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion (HSIL), or presence of neoplasm cells in Pap smear during the first trimester of the gestation.
- Pregnant women in pursuit for squamous epithelial lesions to the moment of the diagnosis of the pregnancy, slopes to treatment definitive, and previous informed consent.
- Pregnant women with cytological diagnosis of benign affections and colposcopy suggestive of cervical dysplasia y/o microinvasive carcinoma, with or without histological confirmation.
- Pregnant women with normal cytology or not included in screening by age, referred to consultation by visible lesion of the cervix, bled post-coitus or persistent vaginal flow, and colposcopy suggestive of cervical dysplasia y/o microinvasive carcinoma, with or without histological confirmation.
- Cytological, colposcopic, and histological pursuits up to 8–12 weeks' post-childbirth.

Three HIV seropositive pregnant was excluded because didn't complete its pursuit post-childbirth, inside the universe of 134 pregnant, not being used sampling.

To all the pregnant women evaluated as new cases in the first trimester, Pap smear and videocolposcopy were carried out, while colposcopy was carried out on those that were in pursuit according to planning. For the prosecution of the colposcopic images was used the version 3.0 of the software to process colposcopic images (SPIC, in Spanish). They were only carried out biopsy among 14-18 weeks in the cases with histological suspicion of high squamous intraepithelial lesion (HSIL) or invasive carcinoma. They were only carried out conization to three patients with colposcopic and histological diagnosis of invasive carcinoma, among 16-22 weeks, previous informed consent and consults of expert.

All pregnant were carried out a cytological and colposcopic control 8 weeks' post-childbirth, being carried out biopsy

for punch directed by colposcopy or cone by handle to the patients that completed the established approaches

The following were considered progression of the cervical epithelial lesion:

- Increase of the lesion degree according to cytological diagnosis and colposcopic correlation.
- Increase of the lesion degree according to correlation of histological and colposcopic diagnoses.
- Increase of the lesion degree according to colposcopic evaluation, according to characteristic of “acetic-white” epithelium, vascular pattern, lesion area, and other specific elements.

Gathering of dates

The clinical histories of all studied patients were revised, being confronted the data of interest with their Cytology, colposcopic images registered in the software SPIC 3.0 and the biopsy, in the Department of Pathological Anatomy of this medical institution.

Variables such as age, risk factors related with the patient’s sexual life, cytological, colposcopic, and histological diagnoses, glandular lesion in cervical channel, extension of the lesion to the channel according to colposcopy, and cytological diagnosis of infection by human papilloma virus confirmed by histology were analyzed.

Prosecution of dates

For statistical analysis, the application Epidat 3.1. The description of categorical variables was carried out with absolute and relative frequencies in percentages. The relationships among categorical variables were analyzed by means of Pearson’s Chi-square test. The exact test of bilateral Fisher is used in the case of not being able to apply the Pearson’s Chi-square test.

To determine the statistical significance was used ($P < 0.05$) according to Cornfield, being carried out an initial univariate analysis that also evaluated the reasons of disparity (odds ratio). The variables that demonstrated significance were subjected to a multivariate analysis of binary logistical regression, leaving a maximum model with the variables and moving away variables for approach of statistical significance (Wald, a step behind). The prediction model was evaluated to Hosmer and Lemeshow test, besides determining its coefficient of determination and the area under receiver operating characteristic curve.

ANALYSIS AND DISCUSSION OF THE RESULTS

More than a third of the cases (38%) were in the age group of 25–29 years, while 24% were in the 20–24 years’ age group

and 18% in the 30–34 years old group. However, significant difference only was founded among the cases with/without progression in the group younger than 20 years, where the risk was of 3.6 times. A third of all the cervical carcinomas occurred during the reproductive period. The incidence of cervical cancer is estimated in 1:1000 and 1:5000 gestations and the biggest challenge constitutes approaching the channel that harbors the development of fetus therapeutically.^[8] Kim^[9] (Munich, 2006–2012) found a median of 33.5 years although almost half of the studied cases were primigestas and Xia-Gao^[10] (2014) found a median of 33.8 years. In this series, the age range is of 15–38 years (26.5 ± 5.3) being considered precocious regarding what reports part of the literature, although some authors like Yu-Mei *et al.*^[11] report a median of 29.8 ± 4.1 years, Khanuja^[12] (India, 2014) report that 78% of their cases were between the age group of 21 and 25 years, and Yue-He^[13] (2013) reported an interval of 20–37 years (29.5 ± 3.7 years). In Cuba, Alina Moré^[14] reported a maximum peak between 25 and 34 years and José Cordero *et al.*^[15] also described a peak of incidence in the third decade of life.

Among the epidemic variables of interest, it is appreciated that seven of 10 patients at least (74%) use intrauterine devices for more than 3 years in the last 5 years, while around the third part of the cases had their first menstruation before 13 years (37%), with their first sexual relationship before the age of 15 years (32%). The use of hormonal anticonception for at least two of the last five years was founded in 26% of patients, tobacco in 20% of them. The 17% referred more than two sexual couples in the last five years and the 11% showed family antecedent of first order of gynecological cancer. Only the first sexual relationship (odds ratio [OR]: $2.5 P = 0.037$) and the antecedent of more than two sexual couples in the last 5 years (OR: $3.4 P = 0.024$) showed statistical significance. In Uruguay, Barrios and Retamoso^[16] found that one of the five cases of their study began sex precociously. In the study of Machain-Loera^[17] in Mexico, when taking like reference to the women that began its sexual life after the 20 years, is considered that those that made it before the 15 years have a risk twice bigger.

Nearly 42% of the pregnant women had a previous childbirth to the current pregnancy, while 35% were nulliparous and 23% only had more than two childbirths. Only in this last group, there was statistical significance (OR: 2.7). Almost 44% of the studied patients had practiced 1–2 previous abortions to the current pregnancy, while 35% reported more than two previous abortions and 21% doesn’t only refer antecedents of abortions. Only in the patients that had antecedent more than two abortions, there was statistical significance (OR: $2.7 P = 0.045$). In Cuba, some authors^[14,15] have shown similar results, nearly 65,45% of the cases with cervical cancer had three or more previous childbirths and the possibility of their appearance is 3,6 times bigger.^[18] In the authors’ opinion,

the multipara's patient is exposed during more time to the relative immunosuppression than it imposes the period of pregnancy, associate or not to high risk serotypes of human papilloma virus and have more probabilities of suffering local traumatism during the delivery.

The analysis of the initial cytological diagnosis leads us to observe that 38% of the patients did not have an altered cytology, while 33% cases had a cytology of low degree (IVPH y/o CIN I), the sixth part (17%), a cytology of high degree (CIN II/III, carcinoma *in situ*), and in smaller frequency, it was patients with benign affections (8%) or with neoplasm cells (micro or invasive carcinoma). The statistical analysis evidenced significance in patients with cytology of high degree (OR: 2.9) and with neoplasm cells (OR: 6.7).

The fourth part of the patients (26%) had a periorificial lesion, while 17% presented a lesion in the anterior lip without affecting the corners, 15% presented lesion in both lips with and without affection in corners (in each case), and 11% presented lesion in anterior lip and corners. Only patients with lesion in the anterior lip and corners (OR: 3.2) and in both lips and corners (OR: 3.4) showed statistical significance.

Although patients that presented with lesion in glandular channel only constituted 39%, this element means a risk 3.2 times bigger than progression. The presence of persistent infection of HPV post-childbirth means a risk 2.5 times bigger than progression of the lesion, being present in 44% of the studied patients.

Nearly 34% of the patients had a lesion lower than 50 mm², while 21% had a lesion of 200 mm² or more and 18% had a lesion in the range of 50–99 mm². In smaller frequency, the patients met with area of lesion of 150–199 mm² (15%) and with area of 100–149 mm² (14%). The patients with lesion area in the range of 150–199 mm² showed a risk 2.1 times bigger than progression and in patients with more area at 199 mm², the risk was 3.2 times that of adults; in both cases, this difference was statistically significant ($P < 0.05$).

More than half of the studied cases (57%) evolved toward the regression, while in 23% of the cases, the diagnosis persisted and in <20%, it progressed to a bigger diagnosis [Table 1]. In the description for diagnoses, 78% of the patients with CIN I showed regression and 7% only progressed. For the CIN II 40% progressed, the same percentage showed persistence and, in 20%, there was regression. For the CIN III, there was justness among cases with progression and persistence (46%) too, for what 9% only had regression. For the carcinoma *in situ*, the progression was evidenced in 67% of the cases and in 75% for the microinvasive carcinoma, not being regression in none of the two diagnoses.

For all diagnosis, except CIN I, were founded significant difference among the cases that progressed or not, increasing the risk from 3.4 for the CIN II, 3.93 for CIN III, 8.1 for the carcinoma *in situ*, and 9.3 for the microinvasive carcinoma. The discoveries of Medina and Oliver Parra^[18] in relation to CIN frequency correspond to other Mexican publications as it is the case of Dr. Torres Lobatón^[19] who in 2007 reported the frequency of the clinical stages and its correlation with the age of the cervical cancer in the General Hospital of Mexico to be CIN 1 (75.2%), CIN 2 (7.2%), and CIN 3 (17.4%). A study published by Yu-Mei et al. in 2014 among 369 pregnant patients found similar proportion of epithelial dysplasia, confirmed by biopsy. These values differ in some aspects that those presented by the author, considering a bigger number of lesions of low degree. This difference could be in relation that several patients began its pursuit before the pregnant and also prevailed young patients, who they spread to prevail the lesions of low degree.

Several authors conclude that pregnancy by itself does not constitute a risk factor carried out with the aggressiveness of the progression of the epithelial neoplasm in this period, since 6–7% should only progress and the rest, to show persistence or regression.^[20] The authors consider that 19.8% of opposing progression triplicates the previous data and it is attributed to the percentages of CIN3, *in situ*, and microinvasive carcinomas, as well as the frequency – also high – of patients with lesions that extend to the cervical canal. A study carried out in Beijing (2014)^[11] showed a progression of 9% among 400 pregnant women, Arteaga and Castellón^[21] in Brazil found a progression of 4.4% and Medina Villaseñor,^[18] who mentions that Melnikow reported progression in 44% of patients with lesions of high degree, while Campos Siccha^[22] reported a regression of 62% in lesions of low degree. The authors consider that these values being different can attribute to the composition of the sample, type of carried out pursuit, form of histological confirmation, and model of evaluation of the progression or regression.

A multivariable analysis of logistical regression with the variables that showed statistical significance was carried out and the results are shown in Table 2. Of the factors only studied, the diagnosis of CIN2+ (OR: 6.7), the lesion with extension to the cervical canal (OR: 4.1), an area of lesion bigger than 149 mm² (OR: 3.8), the persistent infection for HPV after the childbirth (OR: 2.7), and the age younger than 20 years (OR: 2.5) behaved as predictive factors of progression, when reflecting an OR > 1 and a significance ($P < 0.05$).

According to the proposed pattern, a patient with CIN2+ that extends to the cervical canal with a bigger area at 149 mm², persistent infection of the HPV, and younger than 20 years old has 92.7% of probability that his/her lesion progresses to worsening during the gestation.

Table 1: Pregnant women with epithelial lesions by histological diagnosis, Youth Island, 2014-2017

Diagnosis	Cases	Progression (%)	Persistence (%)	Regression (%)
CIN I	90	6 (6.7)	14 (15.6)	70 (77.8)
CIN II	20	8 (40.0)	8 (40.0)	4 (20.0)
CIN III	11	5 (45.5)	5 (45.5)	1 (9.1)
Carcinoma <i>in situ</i>	6	4 (66.7)	2 (33.3)	0 (0.0)
Microinvasive carcinoma	4	3 (75.0)	1 (25.0)	0 (0.0)
Total	131	26 (19.8)	30 (22.9)	75 (57.3)

Source: SPIC 3.0 data

Table 2: Multivariable logistic regression analysis

Variables	EE	P	Odds ratio (CI 95%)	Coefficient
Diagnosis CIN2+	0.873	0.030	6.7 (1.2–16.8)	1.894
Lesion in cervical canal	0.608	0.020	4.1 (1.3–13.3)	1.412
Lesion >149 mm ²	0.636	0.035	3.8 (1.1–13.3)	1.339
Persistent HPV infection	0.624	0.016	2.7 (1.8–9.1)	0.981
Age <20 years old	0.251	0.000	2.5 (1.5–4.1)	0.927
Lesion in the anterior lip or both lips and corners	0.408	0.285	1.5 (0.7–3.4)	0.436
>2 sex couples in the last 5 years	0.215	0.285	1.1 (0.9–2.2)	0.405
Parity >1	0.377	0.396	1.4 (0.7–2.9)	0.321
HSIL or cancer in Pap smear	0.662	0.711	0.8 (0.2–2.9)	-0.246
First sexual relationship before 15 years	0.615	0.318	0.5 (0.2–1.8)	-0.614
Abortions >2	0.597	0.097	0.4 (0.1–1.2)	-0.992

Determination quotient: 0.968. Verisimilitude quotient/Statistical: 84.26 gl: 7. $P=0.002$. Constant (β_0): -4.016. Source: Study data.
 HPV: Human papillomavirus, HSIL: High-grade squamous intraepithelial lesion, CI: Confidence interval

CONCLUSIONS

- Age between 20 and 29 years, antecedents of 1–2 gestations, use of intrauterine devices, precocious menarquia, beginning of sexual relationship before the age of 15 years, and negative cytology or with lesions of low degree were characteristic features found in the sample.
- The histology of CIN2+, lesion in cervical canal, +2 sexual couples in the last 5 years, lesion >149 mm², persistent HPV infection, age younger than 20 years, lesion in the anterior lip or both lips and corners, cytology with HSIL/cancer, parity >1, abortions >2, and the first sexual relationship before 15 years of age showed significant statistical difference among the cases in that progression of the lesions epithelial was identified.
- The presence of CIN2+, lesion in cervical canal, lesion >149 mm², persistent HPV infection, and age younger than 20 years meant a probability of progression of 93%.

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