



Progression Risk of Epithelial Lesions of Cervix in Pregnant, 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 that it has more than enough this phenomenon have the techniques of attended reproduction, the cancer coincidence and pregnancy is supposing an increment, as well as of its precursors lesions. It was carried out a prospective descriptive study to determine the statistical relationship between the progression of epithelial cervical lesions and clinical-epidemic factors of interest in the 131 pregnant assisted in the General Educational Hospital "Baire 'Hero'" during the period 2014-2017. 61% of the patients were 20-29 years of age old, 42% antecedent referred 1-2 childbirths y/o abortions, 74% use of intra-uterine devices, 37% precocious menarquia before 13 years of age, 32% began the sexual relationships before the 15 years and the negative cytology or with lesions of low degree it was present in 71% of the studied sample. The histology of CIN2+, lesion in cervical channel, +2 sexual couples in last 5 years, lesion >149 mm², persistent VPH infection, age smaller than 20 years, lesion in 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 it was identified or non-progression of the epithelial lesions. The presence of CIN2+, lesion in cervical channel, lesion >149 mm², persistent IVPH and age smaller than 20 years meant a probability of progression of 93%.

Keywords: Cancer; Pregnant; Progression

Introduction

The cancer is a strange condition during the pregnancy. This coincidence is estimated in one of each 1000 gestaciones [1]. Every year they are diagnosed in the United States between 3500 and 6000 new cases of wicked illnesses, 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 that it has more than enough this phenomenon have 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.

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

The existent studies of the CIN natural history are limited by several factors: 1°. The CIN confirmation y definitive classification requires biopsy, but this it can alter its natural history, perhaps for induction of a local inflammatory reaction. Some studies, to avoid this possibility, carry out the diagnostic by exam of the cells, but even in combination with the colposcopy, this focus can take place false positive and negative reinforcements, with the subsequent overestimation or underestimate of the progression potential; 2°. The duration 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

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

Diagnosis	Cases	Progress	%	Persist	%	Regress	%
CIN I	90	6	6.7	14	15.6	70	77.8
CIN II	20	8	40	8	40	4	20
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
Microinvasive Carcinoma	4	3	75	1	25	0	0
Total	131	26	19.8	30	22.9	75	57.3

Fuente: SPIC 3.0 data

Table 2: Multivariable logistic Regression logistica.

Variables	EE	p	Odds ratio (IC 95%)	Coef
Diagnosis CIN2+	0.873	0.03	6.7 (1.2-16.8)	1.894
Lesion in cervical channel	0.608	0.02	4.1 (1.3-3.5)	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	2.5 (1.5-4.1)	0.927
Lesion in anterior lip or both lips and corners	0.408	0.285	1.5 (0.7-3.4)	0.436
>2 sex couples in 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

Fuente: Study data

biopsy cannot cover significant lesions and errors of sampling may to take to classify 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.

The Youth's Island, with a global tendency to the increment in the last 15 years, in the triennium 2014-2016, 40% of all the cases of the period 2003-2016 and 57% have been diagnosed in patient younger than 30 years [5-7], over-dimensioned the problem to medical situations not habitual two or three decades behind, as the attention to pregnant and patient without satisfied parity.

The contribution of this investigation can constitute a vital tool in the taking of decisions before one of the common dilemmas that faces to newspaper a kindred doctor to the topic: what to make with a pregnant with cervical epithelial lesions that doesn't owe conizate but to guarantee a sure pursuit. on the other hand, the study of these variables allows to deepen in the knowledge that every day arises in this respect, since they were not enough studies in the country that deepen specifically on this topic, which won't only offer a therapeutic contribution but also diagnosis of this pathology. From the methodological point of view, the present investigation will be good as starting point to other investigators to elaborate future studies related with 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 this way its relapse and the high rate of

mortality for cancer of uterine neck and for ended, to optimize the economic impact on the hospital costs, to achieve a bigger projection to the increase of the natality and not to the unnecessary interruption of gestations and to improve the quality of the population's life.

General objective

To identify relationship between the progression of epithelial lesions of the cervix and clinical-epidemic factors of interest in pregnant assisted in the Hospital General Educational "Baire 'Hero'" during the period 2014-2017.

Goals objectives:

1. To describe the distribution of variables as age groups, previous gestations, factors related with the sexual life and cytological diagnosis.
2. To identify the presence of progression predictors factors in the study sample.
3. To design a prediction model starting from the identified factors.

Design methodological

It was carried out a prospective descriptive study to determine the statistical relationship between the progression of cervical epithelial lesions and clinical-epidemic factors of interest in the 131 pregnant assisted in the General Educational Hospital "Baire 'Hero'" during the period 2014-2017 that completed the inclusion approaches:

- Pregnant assisted in this institution.
- Pregnant with cytological diagnosis of LSIL, HSIL or presence of

neoplasm cells in Pap smear during the first trimester of the gestation.

- Pregnant in pursuit for squamous epithelial lesions to the moment of the diagnosis of the pregnancy, slopes to treatment definitive, previous informed consent.

- Pregnant with cytological diagnosis of benign affections and colposcopy suggestive of cervical dysplasia y/o microinvasive carcinoma, with or without histological confirmation.

- Pregnant 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 pursuit up to 8-12 weeks' post-childbirth.

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

To all the pregnant evaluated as new case in the first trimester was carried out Pap smear and videocolposcopy, while those that were in pursuit were carried out colposcopy according to planning. For the prosecution of the colposcopic images the software SPIC 3.0 was used, what allowed the mensuration of total areas of lesion, lesional area affected by "acetic-white" epithelium or vascular pattern and other studied colposcopic elements. They were only carried out biopsy among 14-18 weeks in the cases with histological suspicion of HSIL or invasive carcinoma. They were only carried out conización to three patients with colposcopic and histological diagnosis of microinvasive carcinoma, among 16-22 weeks, previous informed consent, consults of expert, hospital entrance and strict surveillance of hemostasis and maternal-fetal well-being, not being reported any complication.

To all the pregnant they 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

It was 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 histological and colposcopic diagnosis correlation.

- 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 Card of Cytology, their colposcopic images registered in the application SPIC 3.0 and the tickets of biopsy of the Department of Pathological Anatomy of this medical institution.

Variables were analyzed as age, risk factors related with the patient's sexual life, cytological, colposcopic and histological diagnosis, and glandular lesion in cervical channel, extension of the lesion to the channel according to colposcopy and cytological diagnosis of IVPH confirmed by histology.

Prosecution of dates: For the statistical analysis the application Epidat 3.1 was used. The description of categorical variables is carried out with absolute and relative frequencies in percentages. The relationships among categorical variables are analyzed by means of the test of Chi-square of Pearson. The exact test of bilateral Fisher is used in the case of not being able to be applied the Chi-square test of Pearson.

To determine the statistical significance 95%, it was used ($p < 0.05$) according to Cornfield, being carried out an initial univariado analysis that also evaluated reasons of disparity (odds ratio). The variables that demonstrated significance were subjected to an multivariate analysis of Binary Logistical Regression, leaving of a maximum model with the variables and moving away variables for approach of statistical significance (Wald, a step behind). The obtained prediction pattern was subjected safe against kindness of adjustment of Hosmer and Lemeshow, besides being determined its Coefficient of determination and the area under the Curve of ROC.

Discussion and Result

More than the third part of the cases (38%) they were in the 25-29 years old group, while 24% was in the 20-24 years old group and one of each six patients (18%) in the 30-34 years old group. However, they were only a significant difference among the cases with/without progression in the group of younger than 20 years, where the risk was of 3,6 times adult. A third of all the cervical carcinomas happen during the reproductive period. The incidence of cervical cancer is estimated in 1:1000 and 1:5000 gestations and its biggest challenge constitutes to approach the channel that harbors the development fetal therapeutically [8]. Kirn [9] (Munich, 2006-2012) found a media of 33,5 years old although almost half of the studied cases they were primigestas and Xia-Gao [10] they found a media of 33,8 years old. In this series, the age range is of 15-38 years ($26,5 \pm 5,3$) being considered precocious regarding what reports part of the literature, although some authors like Yu-Mei, et al. [11], report a media of $29,8 \pm 4,1$ years old and Khanuja [12] (India, 2014) with 78% of their cases between the 21 and 25 years of age and Yue-He [13] (2013) with an interval 20-37 years ($29,5 \pm 3,7$ years). In Cuba, Alina Moré [14] reported a maximum pick between 25-34 years and José Cordero, et al. [15] also describes a pick of incidence in the third decade of life.

Inside the epidemic variables of interest, it is appreciated that seven of each 10 patients at least (74%) they use intra-uterine devices for more than three years in the last five years, while around the third part of the cases they had their first menstruation before 13 years (37%) y/o their first sexual relationship before the 15 years (32%). In smaller frequency, the use of hormonal anticonception for at least two of the last five years (26%), tobacco (20%), more than two sexual couples in the last five years (17%) and the family antecedent of first order of gynecological cancer (11%). Only the first sexual relationships (OR: 2,5 $p=0.037$) and the antecedent of more than two sexual couples in the last five years (OR: 3,4 $p=0.024$) they showed statistical significance. Barrios and Retamoso [16] found in Uruguay that one of each five cases of their study began the 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.

42% of the pregnant had a previous childbirth to the current pregnancy, while 35% was nulliparous and 23% only had more than

two childbirths. Only in this last group it was statistical significance (OR: 2,7). 44% of the studied patients had been practiced 1-2 previous abortions to the current pregnancy, while 35% refers more than two previous abortions and 21% doesn't only refer antecedents of abortions. Only in the patients that had as antecedent more than two abortions it was statistical significance (OR: 2,7 $p=0,045$). In Cuba some autores [14,15] has shown similar results, when reporting until in 65,45% of the cases with cervical cancer, three or more previous childbirths, of equal it forms the antecedent of three or more childbirths it increases in 3,6 times the possibility of their appearance what coincides with that outlined by other autores [18]. In the authors' opinion this fact is based in that 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 the HPV, they have more probabilities of suffering local traumatism during the childbirth and that the cervical fabric is each less harmless pregnancy.

The analysis of the initial cytological diagnosis takes us to observe that 38% of the patients didn't 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 patient with benign affections (8%) or with neoplasm cells (carcinoma micro or invasive). The statistical analysis evidenced significance in the 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 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 the patients with lesion in anterior lip and corners (OR: 3,2) and in both lips and corners (OR: 3,4) they showed statistical significance.

Although the patients that presented lesion in glandular channel only constituted the 39%, this element meant a risk 3,2 times bigger than progression. The presence of persistent infection of human papilloma virus in the post-childbirth meant a risk 2,5 times bigger than progression of the lesion, being present in 44% of the studied patients.

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 among 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 among 150-199 mm² showed a risk 2,1 times bigger than progression and in the patients with more area at 199 mm² the risk was 3,2 times adult, in both cases this difference was significant ($p<0,05$).

In the Table 1 are appreciated that more than half of the studied cases (57%) it evolved toward the regression, while in 23% the diagnosis persisted and less than 20% it progressed to a bigger diagnosis. In the description for diagnoses, 78% of the patients with CIN I showed regression and 7% only progressed. For the CIN II 40% progressed, same percentage showed persistence and in 20% there was regression. For the CIN III there was justness among the 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 the diagnosis,

except the slight dysplasia or CIN I had a 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 corresponds to other Mexican publications as it is the case of the Dr. Torres Lobatón [19] who in 2007 it reported the frequency of the clinical stages and its correlation with the age of the cervical cancer in the General Hospital of Mexico in CIN 1 (75,2%), CIN 2 (7,2%) and CIN 3 (17,4%). A study published by Yu-Mei et al. [11] in 2014 found among 369 pregnant patients 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 to that leaves of the patients that are presented in this investigation they were already in pursuit, contributing to the precocity of the diagnosis and also to that also prevailed young patients, where they spread to prevail the lesions of low degree.

Several authors conclude that the pregnancy by itself doesn't 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 patient with lesions that extend to the cervical channel. A study carried out in Beijing (2014) [11] showed a progression of 9% among 400 pregnant, Arteaga and Castellón [21] in Brazil they found a progression of 4,4% and Medina Villaseñor [18], it mentions Melnikow who reported 44% progression in lesions of high degree, while Campos Siccha [22] reported a regression of 62% in lesions of low degree. The authors consider that these values so 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.

When carrying out a multivariable analysis of logistical regression with the variables that showed statistical significance they were the results that they are shown in the Table 2. Of the factors only studied the diagnosis of CIN2+ (OR: 6,7), the lesion with extension to the cervical channel (OR:4,1), an area of lesion bigger 149 mm² (OR: 3,8), the persistent infection for human papilloma virus after the childbirth (OR: 2,7) and the age younger than 20 years (OR: 2,5) they behaved as predictors factors of progression, when reflecting an OR>1 and a significance ($p<0,05$).

According to the proposed pattern a patient CIN2+ that extends to the cervical channel with a bigger area at 149 mm², persistent infection of the human papilloma virus and younger than 20 years old has 92,7% of probability that their lesion progresses to the worsening during the gestation.

Conclusion

1. The age among 20-29 years, the antecedents of 1-2 childbirths y/o abortions, the use of intra-uterine devices, the precocious menarquia, the beginning of the sexual relationships before the 15 years and the negative cytology or with lesions of low degree they were characteristic frequent found in the sample.

2. The histology of CIN2+, lesion in cervical channel, +2 sexual couples in last 5 years, lesion >149 mm², persistent HPV infection, age younger than 20 years, lesion in 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 they showed significant statistical difference among the cases in that it was identified or non-progression of the epithelial lesions.

3. The presence of CIN2+, lesion in cervical channel, lesion >149 mm², persistent HPV infection and age younger than 20 years meant a probability of progression of 93%.

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